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Sensory changes in the territory of the lingual and inferior alveolar nerves following lower third molar extraction

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Abstract

Post-injury inflammation activates nociceptive systems and recruits normally non-nociceptive afferents into a pain processing role. During inflammation, Aβ low threshold mechanoreceptor afferents that usually mediate tactile sensation acquire properties of nociceptors, allowing them to participate in post-injury spontaneous pain and evoked abnormalities such as tenderness and pain to light touch. This study assessed the sensory consequences of post-injury inflammation following extraction of a single, lower third molar tooth. Extensive bilateral evaluations were performed in the territory of nerves assumed to be exposed to both inflammation and mechanical trauma, inflammation alone, or only the central consequences of peripheral inflammation. Testing at the distal termination of nerves assumed to be exposed to local inflammation (mental and lingual nerve territory) revealed decreased detection thresholds ($P < 0.05$) to electrical stimulation and to mechanical stimulation by sensitive, disposable filaments developed and validated for this application. Testing at sites of assumed inflammation and mechanical trauma (mental nerve territory) showed reduced pain thresholds to electrical stimulation. Thermal detection and pain thresholds were not altered at any location in patients, and no effects were observed in control subjects receiving only local anesthetic injections. These results in humans are consistent with recent experimental evidence that inflammatory processes alter the central consequence of activity in large-diameter Aβ touch primary afferents evoked under natural conditions by gentle mechanical stimulation. These effects result in hyperesthesia, increased sensitivity to light touch, and mechanical allodynia, pain evoked by normally innocuous stimulation of Aβ primary afferents.

Keywords: Human; Orofacial; Inflammation; Electrical stimulation; Touch

1. Introduction

Painful conditions are often accompanied by alterations in sensory function. These changes can vary from subtle changes in thermal or mechanical sensitivity to dramatic changes such as mechanical allodynia, cold hyperalgesia, and hyperpathia. There is an increasing recognition that systematic assessment by controlled painful and non-painful stimulation can elucidate peripheral and central mechanisms, and greatly aid diagnosis and possibly evaluation of treatment efficacy. Quantitative sensory testing (QST) can reveal the functional status of myelinated and unmyelinated primary afferents and modulation by central summation mechanisms. QST can quantify mechanical allodynia, in which light touch evokes pain. Most importantly, QST using electrical stimulation can demonstrate conditions in which such tactile pain sensations are mediated by the large-diameter Aβ touch afferents that under normal conditions mediate only non-painful touch sensations. Unlike natural stimulation, electrical stimulation bypasses receptors, directly stimulating primary afferent axons. The Aβ axons are the most sensitive to this stimulation (Collins, 1960;

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Price et al., 1989; Gracely et al., 1996), thus at levels for the threshold for detection, only these fibers are activated. Aβ-mediated mechanical allodynia is indicated if the sensations evoked by usually innocuous electrical stimuli are painful.

Few studies have applied a full QST assessment to the orofacial region. Grushka et al. (1987) evaluated patients with Burning Mouth syndrome and found only decreased tolerance to heat in comparison to normal controls. Studies in patients with trigeminal neuralgia have found increased thresholds to touch, warm and cold (Lewey and Grant, 1938; Nurmikko, 1991; Bowsher et al., 1997; Miles et al., 1997) that are resolved after neurosurgical decompression of the trigeminal nerve root. Dubner et al. (1987) have used mechanical and thermal stimuli to characterize the triggering mechanism in this trigeminal disease.

Results of QST of the orofacial region using electrical stimuli have been variable. Hagberg et al. (1990) used electrical stimuli to evaluate patients with orofacial joint and muscle pain. In comparison to control subjects, patients showed higher detection, discomfort and pain thresholds (decreased sensitivity) to stimuli applied to the skin over the masseter muscle. Within the patient group, those with the greatest spontaneous pain tended to be the most sensitive. However, lower electrical pain thresholds (increased sensitivity) have also been observed in similar patients at both trigger points and areas of referred pain (Vecchiet et al., 1991) and in patients with chronic tension-type headache (Bendtsen et al., 1997).

QST has also been applied to the assessment of acute orofacial pain. Hansson et al. (1988) studied the sensory effects of acute injury by examining mechanical and thermal detection thresholds and heat pain thresholds 5–18 h after oral extraction of a third molar tooth. There was no evidence of increased sensitivity; the only effect was an increased threshold to warm stimuli with a rapid onset rate. Thresholds to warm stimuli with a slower rate were unaffected.

Pain after the immediate phase of acute injury may result mainly from inflammatory processes at the injury site. Recent evidence in rodents suggests that inflammation may actually influence the central consequences of activity in Aβ afferents that normally mediate only non-painful touch sensations. These afferents may change phenotype and behave like nociceptors, releasing substance P and other transmitters from their pre-synaptic terminals (Neumann et al., 1996). The system may also become more sensitive, resulting in activation of flexor motor neurons with decreased Aβ-strength stimulation (Ma and Woolf, 1995). In our own laboratory, we have found that inflammation along the sciatic nerve in the rat increases the sensitivity to electrical and mechanical stimulation (Eliav et al., 1997; Mannes et al., 1997).

Post-operative pain following third molar extraction is predominantly a consequence of inflammation. These inflammatory processes are not observed immediately after surgery, but begin gradually, peaking 2 days after the extraction (Troullos et al., 1990). To our knowledge, the sensory consequences of this acute oral injury, including response to electrical stimulation, have not been examined during this time of maximal inflammatory pain.

With these issues in mind we performed a clinical study in which we evaluated patients before and after local inflammation produced by oral surgical extraction of a single lower third molar tooth. Testing methods included heat and cold detection and pain thresholds, detection and pain thresholds to 10 and 100 Hz electrical stimuli, and detection thresholds to sensitive, disposable monofilament stimulators developed and validated for this application. Sensory evaluation was performed in the territory of several nerves differently affected by the extraction. The inferior alveolar nerve, which innervates the pulp of the extracted third molar, was assumed to be both inflamed and mechanically traumatized by the extraction. The lingual nerve, which branches proximally from the inferior alveolar to innervate the tongue, was assumed to be exposed to inflammatory processes with minimal damage from the extraction. The infraorbital nerve, which emanates from the maxillary branch of the trigeminal nerve, was assumed to be affected only by ganglionic or central consequences of the extraction. In all cases, we tested an area innervated by the terminal branch of the nerve, distal to an assumed inflammation or other process.

2. Subjects and methods

Patients and control subjects were included in the present study after obtaining informed consent under a protocol approved by the NIDR IRB. Patients were examined for pathologies of the oral mucosa, teeth and periodontium and underwent physical examination prior their participation to the study. Patients suffering from systemic disease or any other oral pathology were excluded from the study. The extraction severity was evaluated prior to the extraction; only patients with fully erupted third molars (normally considered a simple extraction) were included in the study. Oral surgery was performed under local anesthesia via a mandibular block of the inferior alveolar nerve (1.8 cc 2% lidocaine with 1:100 000 epinephrine) and conscious intravenous sedation with 2–3 mg midazolam.

Patients (n = 12, four males and eight females, aged 18 to 61 years) participated in three sensory testing sessions: 2 days prior to the extraction of one lower third molar tooth, and 2 and 8 days after the extraction.

Subjects in the control group (n = 6, three males and three females, aged 22 to 48 years) underwent the same sensory testing schedule, and received a mandibular block (1.8 cc 2% lidocaine with 1:100 000 epinephrine) identical to that administered to the patients on the day corresponding to the extraction day in the patient group.

2.1. Sensory tests

The sensory tests, in order of testing, were heat, cold, mechanical, and electrical detection thresholds, followed by electrical, heat and cold pain thresholds, and pain intensity ratings. Tests were performed within the lingual nerve territory on the anterior two-thirds of the tongue (LNG), within the inferior alveolar nerve territory, on the middle third of the buccal surface of the first intact premolar tooth (PM), and at the termination of the nerve (mental nerve territory) located on the skin under the lower lip (MNT). Electrical stimuli were assessed within two additional sites in the infraorbital nerve territory (maxillary branch of the trigeminal nerve): on the skin above the upper lip (UL) and on the skin in the infraorbital foramen area (IO). Control subjects also received electrical tests on the left volar forearm (FA). Tests on the face were performed on both the extracted and the non-extracted sides.

2.2. Thermal detection and pain thresholds

Detection thresholds for warm and cool, and pain thresholds for cold and heat pain, were evaluated by a 5×5-mm water-cooled Peltier probe (Medoc TSA 2001). Detection thresholds were assessed at LNG, MNT and PM using a staircase paradigm in which stimulus intensity was alternately increased (increased temperature for warm trials, decreased temperatures for cool trials) on successive trials until a sensation was evoked, and decreased until no sensation was experienced. After each change in direction, the amount of stimulus change from each trial was reduced by half, and the ascending and descending trials were repeated until this increment was reduced to 0.1°C. In this series the starting temperature was 32°C and the starting increment was 3.0°C.

Pain thresholds were determined in the MNT territory using an ascending (from no pain to pain) Method of Limits for both heat and cold pain. Continuous ramp (1°C/s) stimuli from a baseline of 32°C were increased (limit of 50°C) or decreased (limit of 8°C) until a report of pain. The pain threshold was computed from the average of five trials.

We could not evoke pain in either the LNG or PM site with brief thermal stimuli between 8°C and 52°C. Pain sensitivity in these areas was assessed by collecting suprathreshold judgments of pain intensity using Gracely box scales (Coghill and Gracely, 1996; Hostetter and Gracely, 1997) at 15-s intervals during 60 s of either 8°C (cold pain) or 52°C (heat pain) continuous stimulation. These scales are 0–20 vertical numerical category scales, enclosed in stacked squares. Superimposed is a list of verbal descriptors of the sensory intensity or unpleasantness of pain sensations, positioned at appropriate vertical intervals by means of previously validated values for each descriptor (Gracely et al., 1978a,b, 1979).

2.3. Mechanical detection threshold

The orofacial region is very sensitive to mechanical stimulation. In order to maintain appropriate body fluid precautions, we developed sets of sensitive, disposable mechanical stimulators. The force applied by different lengths (0.5, 1.0, 1.5, 2.0 and 2.5 inch) of Proline 7-0 monofilaments (Ethicon) suture line was measured eight times for each of five filaments of each length. For each measurement, a filament was grasped at the end by forceps and the other end was positioned perpendicular to a laboratory balance, applying enough force to place a slight bend in the filament.

Mechanical detection was assessed in the patients by administering the series of filaments two times each in ascending order. With eyes closed, patients indicated each time a filament touch was detected at the MNT, LNG, IO and UL territories. The lowest force resulting in a consistent positive was defined as the detection threshold.

2.4. Electrical detection and pain threshold

Continuous trains of constant current electrical stimuli were delivered to the skin or mucosa through 8-mm diameter spherical gold-plated electrodes spaced 23 mm apart. Stimulus frequency was varied between 10 and 100 Hz with a 50% duty cycle. Polarity of the electrodes was randomized. During tongue stimulation the tongue was extended, and dried and isolated by 2×2-inch cotton gauze pads.

Electrical detection and pain threshold were assessed in the MNT, LNG, IO and UL territories on the extracted and the non-extracted sides in patients and on the injected and non-injected sides, and also in the FA, in the control subjects. Detection and pain thresholds were assessed on separate trials by ascending Method of Limits. Stimulating current was increased slowly until the subject indicated detection or pain. Two detection and pain thresholds were evaluated for both 10-Hz and 100-Hz stimuli for each location.

2.5. Data analysis

Threshold or ratings for each modality were evaluated by overall analysis of variance. Planned paired *t*-tests between the extracted and control sides were performed for each modality. Wilcoxon tests were performed if the data did not meet the normality assumptions required for *t*-tests. Except where noted, data are summarized as mean ± standard error.

3. Results

3.1. Mechanical detection threshold

Fig. 1 shows the results of repeated trials in which the

force produced by five filaments of each length were measured eight times. As shown in the figure, the forces ranged from 72.15 ± 0.99 (standard deviation) mg for 0.5-inch filaments to 2.25 ± 0.16 mg for 2.5-inch filaments.

Fig. 2 shows the results of mechanical testing. Overall analysis of variance and analysis of only the baseline day showed a significant effect of location ($P < 0.005$, $P < 0.01$) due to decreased sensitivity in the lingual territory. Two days after the extraction, the detection threshold for mechanical stimulation was decreased from the contralateral control value in the territory of the mental (2.71 ± 0.30 mg, 4.57 ± 0.85 mg, $P < 0.05$) and lingual (7.08 ± 2.19 mg, 12.30 ± 2.62 mg, $P < 0.05$) nerves. An inspection of individual responses at this time showed that within the limits of the stimulators, a difference could be detected in five subjects following mental stimulation and in six subjects following lingual stimulation. No subject showed greater sensitivity on the control side. No other effects were observed at this time in the other nerve territories, or at any location at 8 days after the extraction.

3.2. Electrical detection threshold

Fig. 3 shows electrical detection thresholds for all days, groups and frequencies. Separate analyses of variance and analysis of only the baseline day for both the control and extraction groups showed a significant effect of location ($P < 0.01$) due to decreased sensitivity in the lingual territory. Two days after the extraction, the threshold for detection of electrical stimulation at both frequencies was significantly reduced in comparison to the contralateral control value in the territory of the mental (10 Hz: 18.8 ± 3.0 μA, 27.5 ± 2.0 μA, $P < 0.05$; 100 Hz: 19.5 ± 3.0 μA, 26.2 ± 2.0 μA, $P < 0.05$) and lingual (10 Hz: 28.5 ± 6.0 μA, 51.4 ± 12.0 μA, $P < 0.05$; 100 Hz: 30.0 ± 5.0 μA, 65.0 ± 14.0 μA, $P < 0.05$) nerves. Inspection of individual responses showed that these differences were observed in most subjects: in the mental territory one subject showed an opposite response of increased sensitivity on the control side (0.1 μA) at 10 Hz and three subjects showed an opposite response (0.25, 0.4, 0.5 μA) at 100 Hz, in the lingual nerve territory, one subject showed an opposite response at 10 Hz (0.15 μA) and no subject showed an opposite response at 100 Hz. No other effects were observed at this time in the other nerve territories, or at any location at 8 days after the extraction in either group.

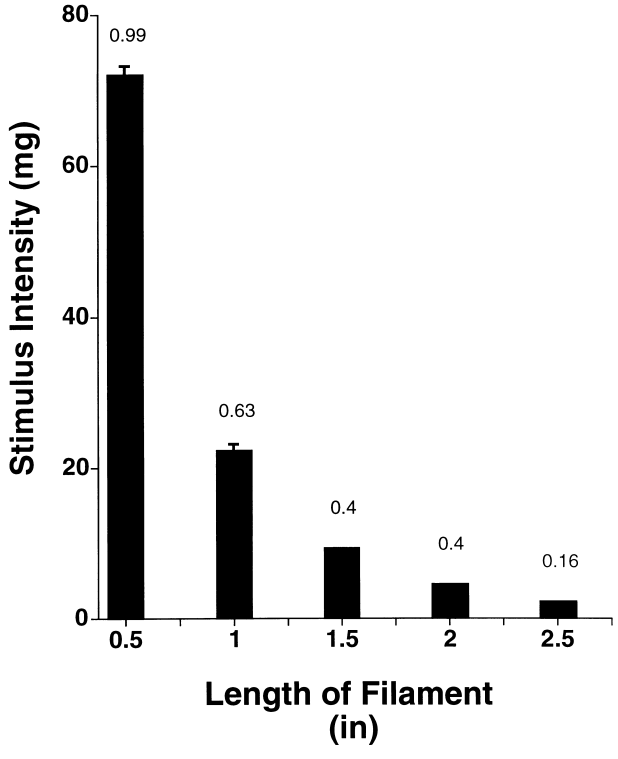

Fig. 1. Calibration of disposable mechanical stimulators. Force in mg is plotted against length of prolene blue monofilaments cut from 7-0 suture material. Five filaments of each length were calibrated by clamping one end in a hemostat and pressing the opposite end of each filament against an electronic lab balance with a force sufficient to cause a slight bend in the filament. Forty trials for each set of filaments (eight per filament) were averaged. Mean force and standard error are shown for the five filament lengths used in the study.

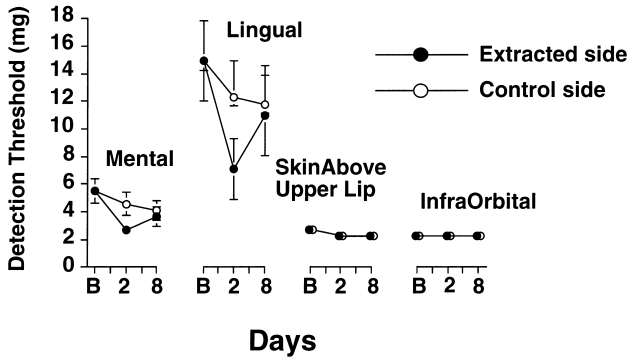

Fig. 2. Mechanical detection threshold. Stimulus force in mg and standard errors are plotted against days (pre-operative baseline and 2 and 8 days post-surgery) for the mental, lingual, cutaneous upper lip and infraorbital nerve territories. In comparison to the control side, detection thresholds were significantly lower ($P < 0.05$) on the extracted side 2 days after surgery for both the mental and lingual nerve territories.

3.3. Electrical pain threshold

Fig. 4 shows electrical pain thresholds. Separate analyses of variance and analysis of only the baseline day for both the control and extraction groups showed a significant effect of location ($P < 0.01$) due to decreased sensitivity in the lingual territory. Two days after the extraction, the electrical pain threshold for both frequencies was reduced in comparison to the contralateral control in the mental nerve territory. This difference was significant for 10 Hz (46.0 ± 8.0 μA, 63.2 ± 9,0 μA, $P < 0.05$) and approached significance for 100 Hz (44.0 ± 7.0 μA, 63 ± 10.0 μA, $P = 0.0505$). Individual data revealed a consistent effect across subjects with only two exceptions. One subject showed a strong contrary effect of increased sensitivity on the control side (4.05 μA at

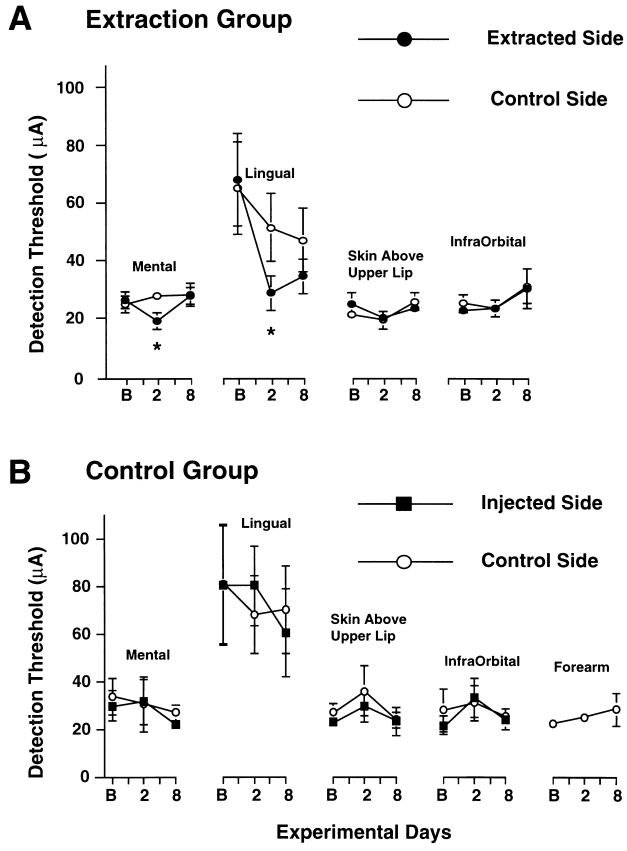

Fig. 3. (A,B) Electrical detection thresholds to 100 Hz stimulation. The top panel shows the results for the extraction group. Stimulus current in μA and standard errors are plotted against days (pre-operative baseline and 2 and 8 days post-surgery) for the mental, lingual, cutaneous upper lip and infraorbital nerve territories. In comparison to the control side, detection thresholds were significantly lower ($P < 0.05$) on the extracted side 2 days after surgery for both the mental and lingual nerve territories at both stimulus frequencies. The bottom panel shows electrical detection thresholds for the control group receiving a local anesthetic block of the descending mandibular branch of the trigeminal nerve. Stimulus current in μA and standard errors are plotted against days (pre-operative baseline and 2 and 8 days post-injection) for the mental, lingual, cutaneous upper lip and infraorbital nerve territories. In comparison to the control side, detection thresholds were unaltered on the injected side at any time or location. Evaluation at 10 Hz showed the same effects.

10 Hz, 3.1 μA at 100 Hz), while another subject showed a weak contrary effect (0.2 μA at 10 Hz, 0.1 μA at 100 Hz). No other effects were observed at this time in the other nerve territories, or at any location at 8 days after the extraction in either group.

3.4. Thermal tests:

The detection thresholds (32°C baseline) in the teeth were higher for heat (32.8–42.0°C) and lower for cold (19.6–22.9°C) compared to the mental (heat: 33.1–33.3°C; cold: 31.1–31.3°C) and lingual (heat: 34.0–34.9°C; cold: 30.3–30.9°C) nerve territories. This difference did not reach statistical significance, although an overall analysis of variance revealed a significant main effect of the warm thresholds for days ($P < 0.05$) and a significant interaction of time with location ($P < 0.05$). These effects can be accounted for by an increase in the warm threshold in teeth over days that was similar for both the extracted and control sides. In addition, the cold detection thresholds showed a trend for an effect of location ($P = 0.08$) that can be accounted for by the variable higher (lower temperature) cold detection threshold in teeth. Other than these effects, there was no significant difference between the extracted and the non-extracted side before, and 2 and 8 days after, the extraction at any location.

Pain thresholds for thermal stimuli applied to the mental nerve territory were 12.7–13.7°C for cold. Heat pain thresholds were 42.6–42.9°C on the baseline days and 46.8–

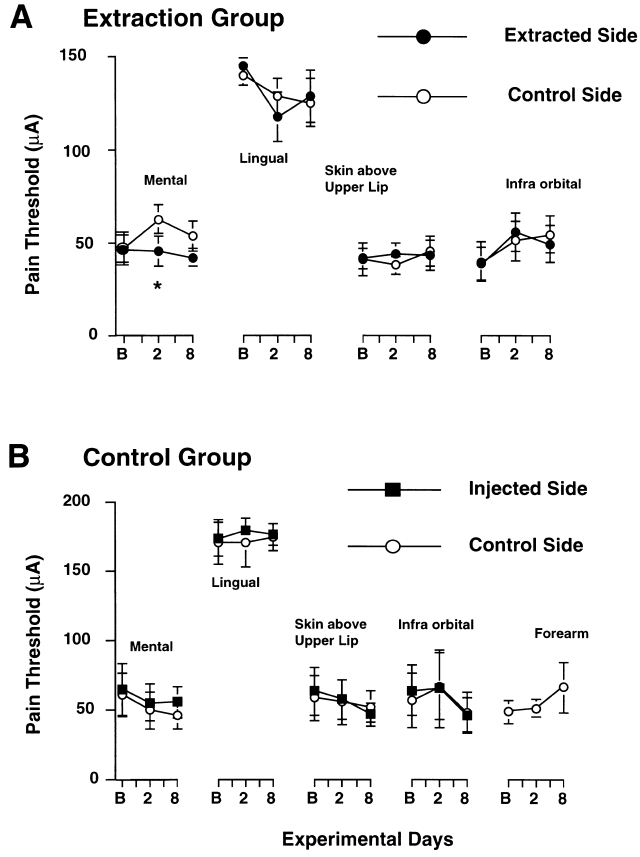

Fig. 4. (A,B) Electrical pain thresholds to 100 Hz stimulation. The top panel shows the results for the extraction group. Stimulus current in μA and standard errors are plotted against days (pre-operative baseline and 2 and 8 days post-surgery) for the mental, lingual, cutaneous upper lip and infraorbital nerve territories. In comparison to the control side, detection thresholds were significantly lower ($P < 0.05$) on the extracted side 2 days after surgery for the mental nerve territory at both stimulus frequencies. The bottom panel shows electrical pain thresholds for the control group receiving a local anesthetic block of the descending mandibular branch of the trigeminal nerve. Stimulus current in μA and standard errors are plotted against days (pre-operative baseline and 2 and 8 days post-injection) for the mental, lingual, cutaneous upper lip and infraorbital nerve territories. In comparison to the control side, pain thresholds were unaltered on the injected side at any time or location. Evaluation at 10 Hz showed the same effects.

48.3°C on the post-operative days. There was no significant change between the extracted and control side at any time point, nor effect of days.

The ratings of 60-s duration stimuli applied to the premolar region ranged from 3.5 to 6 (very weak to very mild) for both heat and cold stimulation. Ratings for stimuli applied to the lingual nerve territory on the tongue ranged from 15.1 to 17.7 (strong to very intense) for heat stimuli and from 6.7 to 9.4 (very mild to mild-moderate) for cold stimuli. There was no difference between the extracted and control side at any time or location.

4. Discussion

4.1. Mechanical and electrical stimulation reveal increased large fiber sensitivity

The striking feature of the present study is that sensations mediated by the large diameter Aβ afferents were altered 2 days after oral surgery. Under normal conditions, Aβ low threshold mechanoreceptors mediate light touch. The sensitive mechanical stimulators we developed indicated increased innocuous tactile sensitivity in the territory of both the mental and lingual nerves.

This increased tactile sensitivity is likely due to altered sensitivity to input from Aβ touch afferents, although the results of mechanical stimuli alone cannot rule out a contribution from smaller fibers. As we noted previously, the large diameter axons normally activated by these mechanical stimuli are also the most sensitive to electrical stimulation, irrespective of changes in receptor sensitivity. We observed that the stimulating current required to produce a just detectable sensation was less in the ipsilateral territory of both the mental and lingual nerves 2 days after surgery. This result supports the findings observed with mechanical stimulation and strongly suggests that the increased sensitivity is mediated by Aβ afferents. This effect appears similar in the terminal branches of both the lingual and mental nerves, which were exposed proximally to different consequences of oral surgery. The lingual nerve was likely exposed to inflammatory processes but not directly damaged by the oral surgery. In contrast, the mental nerve was subjected to mechanical trauma with peripheral and potential central consequences. Extirpation of the tooth pulp initiates central processes of degeneration and reorganization (Gobel and Binck, 1977; Gobel, 1984) that may influence sensitivity during this early post-operative period. Despite the localized mechanical trauma, the mental nerve may be relatively less exposed to inflammatory processes. The inferior alveolar nerve travels in a bony canal, relatively protected from distant inflammatory events. Inflammatory mediators may gain access through the foramen that allow termination in the tooth pulp, a relatively small access compared to the large potential exposure of the lingual nerve.

Detection thresholds for mechanical and electrical stimulation of the upper lip and infraorbital region, which are innervated by maxillary branch of the trigeminal nerve, were not altered by oral surgery. This result suggests the effect of tooth extraction on Aβ afferents was confined to the mandibular branch of the trigeminal nerve. The data show a non-significant trend for increased sensitivity in the contralateral lingual nerve territory, suggesting a possible bilateral effect that would be mediated centrally. However, the control subjects show a similar trend in the contralateral lingual territory but not in the volar forearm. Thus, the trend for a decrease in contralateral lingual detection thresholds may represent increasing performance in the difficult task of lingual sensory detection. The contralateral difference in thresholds likely represents an increase in orofacial Aβ sensitivity, produced by consequences of oral surgery that may include local inflammation, which is superimposed on this trend for increased detection performance.

The increased detection thresholds to mechanical and electrical stimuli found 2 days after surgery were not observed by Hansson et al. (1988) in the immediate (5–18 h) post-operative period. This difference suggests that the sufficient condition for increased mechanical sensitivity is the post-operative inflammation which likely peaks at the time of our tests at 2 days post-surgery (Troullos et al., 1990). The pain and tissue trauma in the immediate post-operative period may be insufficient to alter mechanical sensitivity. It is also possible that lingering effects of operative medications or activation of endogenous process may mask such an effect.

In contrast to detection thresholds, differences in the electrical pain threshold were observed only in the territory of the injured, mental, nerve. This specificity suggests that increased pain sensitivity to electrical stimulation may indicate prior nerve damage in the territory of that particular nerve. Unfortunately, this specificity does not imply a specific underlying mechanism. It is not clear from our results if the difference represents increased electrical pain sensitivity in the ipsilateral mental territory or a decreased sensitivity in the contralateral mental territory. In addition, the lack of a difference in the lingual territory could represent no alteration in sensitivity, or a generalized bilateral effect in which central mechanisms result in increased pain sensitivity (decreased thresholds) in the entire bilateral lingual nerve distribution.

These human results are consistent with studies of inflammation in rodents. Injection of CFA into the hind paw of the rat results in decreased mechanical withdrawal threshold and increased neural responses to innocuous touch and to noxious pinch stimulation (Ma and Woolf, 1996a). In our laboratory, we found that confining the inflammation to the nerve trunk produced similar effects (Eliav et al., 1997). In this experimental model of neuritis, inflammatory agents CFA or carrageenan are applied to the sciatic nerve. The ipsilateral paw demonstrated increased sensitivity to both mechanical stimulation and to the same 10- and 100-Hz

electrical stimuli used in the present experiment. The time course of increased paw sensitivity was also similar to the present human result. The hyperesthesia was observed 2 days after the initiation of inflammation, persisted for 3 days, and returned to normal by 6 days. These studies in the human and the rat provide converging lines of evidence that inflammation along a nerve results in increased sensitivity to input from large-diameter Aβ afferents. This altered sensitivity may serve as a marker for this inflammation, indicating both the magnitude and time course of the inflammation.

In addition, recent studies have indicated that inflammation changes the character as well as the sensitivity of Aβ afferents. Aβ afferents undergo a phenotypic switch in which they acquire properties of nociceptors, releasing substance P at their pre-synaptic terminals and increasing the excitability of central neurons (Neumann et al., 1996; Woolf, 1996). Once inflammation is present and Aβ sensitivity is increased, gentle mechanical stimulation results in a progressive increase in innocuous and noxious tactile sensitivity (Ma and Woolf, 1996a). This increase is accompanied by changes in *fos* expression usually observed with noxious stimulation (Ma and Woolf, 1996b), and is blocked by tachykinin NK_1 receptor antagonists (Ma and Woolf, 1997). Although this progressive tactile hypersensitivity was not evaluated in the current protocol, identification of such an effect in future studies may provide an additional marker for inflammatory etiology in idiopathic orofacial conditions.

The hyperesthesia observed in the lingual nerve territory in this study and in animal models (Ma and Woolf, 1996a; Eliav et al., 1997) represent cases of neural inflammation with minimal nerve damage. As noted above, the results in the mental nerve territory, which was exposed to a greater degree of nerve damage, differed from those found in the lingual nerve territory; the mental nerve showed electrical hyperalgesia at 2 days that had waned by 8 days. These effects are similar to the effects observed following chronic constriction injury (CCI) to the sciatic nerve in the rat (Mannes et al., 1997). This extensive nerve damage results in electrical hyperalgesia at 4 days that disappears by 9 days. However, this model may not parallel our clinical findings; the massive sciatic damage greatly exceeds the minor damage of tooth extraction, and the later hypoesthetic period observed in the rat likely represents the destruction of Aβ innervation. Comparison of our findings to other animal models of minor nerve damage may reveal effects consistent with our observations of lowered electrical pain thresholds in the mental nerve territory.

4.2. Thermal stimulation suggests unaltered small fiber function

Both pain and thermal sensations are mediated by populations of thinly myelinated Aδ fibers and unmyelinated C-fibers. Oral surgery did not alter any response to either non-noxious or noxious thermal stimuli, strongly suggesting that there was no effect of oral surgery and subsequent inflammation on small primary afferent fibers.

The absence of heat hyperalgesia in areas removed from the extraction site is consistent with a body of human experimental evidence showing a lack of secondary heat hyperalgesia following a burn (Raja et al., 1984; Dahl et al., 1993) or intradermal injection of capsaicin (Gracely et al., 1993a,b; Ali et al., 1996). Reports of restricted heat secondary hyperalgesia following capsaicin (LaMotte et al., 1991; Serra et al., 1993) may be explained by mechanical stimulation by contact stimulators or extension of the area of primary heat hyperalgesia (Ali et al., 1996). The absence of a change in heat sensitivity in secondary areas is also consistent with minimal findings of secondary heat hyperalgesia in subjects with peripheral neuropathic pain syndromes now classified as CRPS-1 (Ochoa, 1986; Cline et al., 1989; Gracely et al., 1992; Price et al., 1992; Bennett, 1994; Janig and Stanton-Hicks, 1996). These experimental and clinical conditions have been shown to result from central sensitization to noxious and innocuous input. Considerable evidence from animal and human experimental studies indicates that this central sensitization is initiated, and clinical studies indicate that it is maintained and modulated, by persistent input from nociceptors (Woolf and Wall, 1986; Woolf and Thompson, 1991; Gracely et al., 1992; Bennett, 1994; Koltzenburg et al., 1994). The central excitability in both CRPS-1 and human capsaicin models modulates input from adjacent regions (LaMotte et al., 1991; Price et al., 1992; Torebjörk et al., 1992; Gracely et al., 1992, 1993a,b; Bennett, 1994; Koltzenburg, 1996). However, this central process does not appear to alter the sensitivity of input from Aδ- and C-fiber heat nociceptors in these adjacent secondary regions.

The sensitivity of the small fibers that mediate non-noxious thermal sensations also were not altered following oral surgery. This result is consistent with previous findings of Hansson et al. (1988) who found unchanged cold and warm thresholds 5 to 18 h after oral surgery. A second measure of the warm threshold, reaction time to a fast-rise time stimulus, actually showed decreased sensitivity which may have indicated activation of diffuse inhibitory systems (DNIC, Le Bars et al., 1979).

Unaltered thresholds of Aδ-mediated cool sensation and C-fiber-mediated warm sensation are found also in cases of central sensitization with one possible exception. Many patients with CRPS-1 report cold allodynia and cold hyperalgesia; contact with room temperature metal objects is distinctly painful. Cold allodynia and hyperalgesia have not been reported in studies administering the usual dose of 100 μg intradermal capsaicin, but have been observed after administration of higher doses ranging from 250 to 1000 μg (Gracely et al., 1993a,b). Thus cool/cold sensation may be altered clinically only in conditions in which the initiating and maintaining input is sufficiently intense. The mechanism(s) of cold hyperalgesia is not known with certainty. There is accumulating evidence for small-fiber

mechanisms (Ochoa and Yarnitsky, 1994; Campero et al., 1996; Hao et al., 1996) and also possible mediation by large fibers (Frost et al., 1988).

4.3. Reduction of electrical detection and pain threshold

The observation in the territory of the mental nerve that both electrical detection and pain thresholds were reduced indicates two separate effects of the central processes. The first is the facilitation of non-painful mechanical sensitivity. The second is the translation of a previously non-painful sensation into a distinctly painful sensation. These effects could occur by a common or separate mechanism. The negative results with thermal stimulation suggest that only the Aβ input is affected. The most parsimonious explanation is a facilitation of Aβ input that results in increased tactile sensitivity at low levels and, at sufficient levels, results in a painful quality. These Aβ effects could span a continuum from slight changes in Aβ tactile sensitivity to full-blown allodynia in which activation of only a minimal number of Aβ afferents (such as those innervating a guard hair) evokes an intense pain sensation. The present finding of lowered pain threshold without allodynia may be an example of an intermediate level in which the synchronous barrage produced by electrical stimuli produces Aβ-mediated pain while natural mechanical stimulation is not sufficient.

4.4. Conclusion

Altered sensitivity to mechanical and electrical stimulation has been observed in syndromes involving nerve injury referred to as reflex sympathetic dystrophy and now CRPS-I. More subtle alterations have been observed in other less-disabling conditions, and found in this study after assumed post-operative inflammation. Similar results of increased sensitivity to weak electrical stimuli have been observed in animal models of nerve inflammation (Ma and Woolf, 1996a; Eliav et al., 1997). These changes in sensitivity are likely due to central processing of the large diameter, fast-conducting Aβ low-threshold mechanoreceptor primary afferents that normally mediate the sense of light touch. The present results suggest a continuum of effects from the normal condition to frank Aβ-mediated allodynia and hyperalgesia. Between these extremes, minor nerve injury and/or inflammation may initiate and maintain central processes that increase the sensitivity to Aβ stimulation but are insufficient to evoke the central processes responsible for robust allodynia. Our data suggest that inflammation evokes Aβ hyperesthesia, while the nerve injury of pulp extirpation produces lowered electrical pain thresholds. These effects appear to be manifested during the period of maximal inflammation, although factors other than inflammation could logically account for these results. Our next study concerns manipulating post-operative inflammation to assess the role of inflammatory processes in the observed sensory changes. The present results in humans are consistent with the results of basic studies of inflammation-induced increases in tactile sensitivity and altered processing of input from Aβ afferents. The results also suggest that controlled electrocutaneous stimulation may provide an especially sensitive tool for diagnosis and evaluation of orofacial and other chronic pain conditions.

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